

The Use of Copper Intrauterine Devices (IUDs) to Treat Antimicrobial-Resistant Infections in Mares

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Introduction

Purpose: Development of a one-time application of a drug-free intrauterine device (IUD) to control antimicrobial resistant bacteria

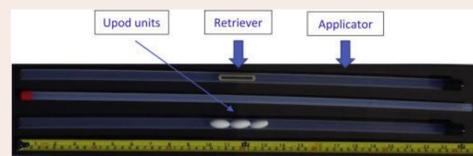
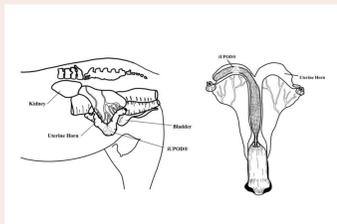


The rise in antimicrobial resistance (AMR) is an urgent concern in both human and veterinary medical fields. AMR infections are challenging to treat and create the need for the development of drug-free treatment and preventative methods. This is especially apparent within obstetrics and gynecology due to the female genital tract being prone to infections caused by more than one microbe.

The antimicrobial effects of copper were first noted by Egyptians in 2600BC, and recent studies have shown the metal to be effective against bacteria, fungi, and viruses in clinical settings. In this study, we assess the use of copper in novel equine IUDs (iUPODs) to treat AMR uterine infections in mares. Bacterial infections of *Pseudomonas aeruginosa* (*P. Aeru*) and *Streptococcus zooepidemicus* (*S. Zoo*) were used as models.

Materials and Methods

This was a 90-day pilot study incorporating clinical work at the UMass Hadley Farm as well as lab work on the UMass campus. Novel equine IUDs, called iUPODs, were used in this study. Each iUPOD consists of three units of cylindrical plastic-coated magnets. For contraceptive purposes, all three units must be inserted into the uterus of each mare. This study assessed the use of only inserting one or two units for antimicrobial treatment when contraceptive purposes are not necessary.



- 7 mares at the Hadley Farm were inoculated with *P. Aeru* and clinical signs of infection were monitored weekly by ultrasound. Uterine swabs were taken every 30 days and were streaked on blood agar to monitor bacterial growth. **Note:** No *P. Aeru* infections developed, so mares were inoculated with *S. Zoo*.
- All mares received one iUPOD unit by Day 60. **Note:** Some mares received additional units between Day 60 and Day 90.
- All iUPOD units were removed on Day 90.

Results

	Growth? Yes or No			
	Day 0	Day 30	Day 60	Day 90
Jessie	no	no	yes	no
Emma	no	yes	yes	yes (less)
Red	yes	yes	no	no
Enchanted	no	no	no	no
Legacy	no	no	no	no
Valentine	no	no	no	no
Y. Rose	no	no	no	no

Table 1: Growth from uterine swab streaks on blood agar after 48-hour incubation at 37°C

	Number of iUPOD Units	
	Day 60	Day 90
Jessie	1	3
Emma	1	3
Red	1	1
Enchanted	1	1
Legacy	1	2
Valentine	1	1
Y. Rose	1	1

Table 2: Comparison of number of iUPOD units in each mare on Day 60 (when iUPODs were inserted) to Day 90 (last day of project)

Day 0: Bacterial growth was observed from Red's uterine swab culture. This was determined to be *Escherichia coli* upon PCR testing. No other growth was observed from the other mares. Mares with bacterial positive culture were further screened for yeast and no growth was found.

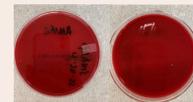


Figure 1: Emma's Day 0 uterine swab culture

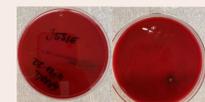


Figure 2: Jessie's Day 0 uterine swab culture

Day 30: Growth from Emma's uterine swab culture was observed and determined to be *S. Zoo*. This was likely facilitated by a cervical defect. Red's culture grew *E. Coli*, and no growth was observed from the other mares. No mares contracted infections from Day 0 *P. Aeru* inoculations.

Note: Emma contracted an *S. Zoo* infection prior to *S. Zoo* inoculation.



Figure 3: Emma's Day 30 uterine swab culture

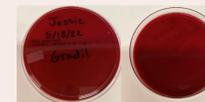


Figure 4: Jessie's Day 30 uterine swab culture

Day 60 (Post *S. Zoo* inoculation, pre-iUPODs): Jessie's and Emma's cultures grew *S. Zoo*. Red's culture no longer showed any growth, and no growth was observed from the other mares.

NOTE: Legacy lost her single iUPOD unit shortly after it being inserted on day 60. Two iUPOD units were inserted, which she retained through day 90. Enchanted and Valentine both lost their one iUPOD unit by day 90.



Figure 5: Emma's Day 60 uterine swab culture



Figure 6: Jessie's Day 60 uterine swab culture

Day 90 (post-iUPODs): Jessie and Emma's infections persisted after one iUPOD unit was inserted but subsided shortly after 2 additional units (3 units total) were administered to both mares. By day 90, these mares presented no clinical signs of infection upon ultrasound. No growth was observed from Jessie's culture and less growth was observed from Emma's culture when compared to day 60.



Figure 7: Emma's Day 90 uterine swab culture

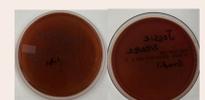


Figure 8: Jessie's Day 90 uterine swab culture

Discussion and Future Directions

- The reduced bacterial growth and absence of clinical signs of infection after the introduction of iUPODs to Jessie and Emma suggest that copper iUPODs may successfully treat uterine infection.
- The lack of improvement until all three units were introduced suggests a higher copper concentration than that of one single unit may be necessary to combat bacterial infection in some mares.
- The loss of iUPOD unit by 3 out of 5 mares given 1 unit suggests that at least 2 units may be necessary to ensure iUPOD retention. Please note that this was a set 90-day preliminary study and additional data must be collected before definitive conclusions can be made.



Additional studies are currently underway such as monitoring how iUPODs affect progesterone levels in mares.

References

- Ardenon, Linda P., Thakar, Renee, & Sultan, Abdul H. (2019). The use of copper as an antimicrobial agent in healthcare. *Clinical Microbiology R Reviews*. 2019:35
- Gradil, Carlos M., Uricchio, Cassandra K., Schwarz, Allison. Self-Assembling Intrauterine Device (Upod) Modulation of the Reproductive Cycle in Mares. *J Equine Vet Sci*. 2019:83

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